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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,345	12/12/2003	Aris N. Economides	REG 132B1-C	6824

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,345	ECONOMIDES ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10,11 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 10, 11, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment of 27 February 2007 has been entered in full. Claims 3-9 and 12-19 are canceled. Claims 1, 2, 10, 11, and 20 are under examination.

Withdrawn Objections And/Or Rejections

The requirement for a new oath or declaration as set forth at p. 2 of the previous Office Action (mailed 28 November 2006) is *withdrawn* in view of the newly submitted declaration (received 27 February 2007).

The rejection of claim 11 under 35 U.S.C. § 112, second paragraph, as set forth at pp. 2-3 of the previous Office Action (mailed 28 November 2006) is *withdrawn* in view of the amended claim (received 27 February 2007).

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 10, 11, and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis of this rejection can be found at pp. 3-5 of the

previous Office Action (mailed 28 November 2006). It is noted that the amendments to the claims have overcome the enablement issue regarding the scope of the noggin polypeptides to be administered (i.e., the issues raised at p. 5, last paragraph, to middle of p. 7).

Applicant's arguments (pp. 5-10 of response received 27 February 2007) have been fully considered but are not found to be persuasive for the following reasons. Applicant argues that a *prima facie* case for nonenablement has not been made in that the examiner has failed to provide a rational explanation to doubt the veracity of Applicant's evidence for enablement. Applicant argues that the examiner has raised the patentability bar by requiring working examples. Applicant urges that this standard is legally incorrect, arbitrary, and insurmountable without completion of an FDA-approved Stage III clinical trial. This has been fully considered but is not found to be persuasive. A rational explanation of nonenablement has been made I the previous Office Action, mailed 28 November 2006. Beginning at p. 3, this action sets forth:

> The specification asserts that noggin polypeptides are effective to treat BMP-related disorders such as fibrodysplasia ossificans progressive (FOP). No working examples directed to protein therapy of patients already suffering from FOP or any other BMP-related disorder are provided. The specification discloses that gene therapy with nucleic acids encoding noggin protected mice against ossification upon subsequent treatment with a BMP-4 implant. However, this working example does not speak to how a noggin *polypeptide* would affect a patient *already suffering from a bone disorder*, as recited in the claims. It is known in the art that noggin is an antagonist of BMP-4, and that BMP-4 is involved in FOP. See Zimmerman et al. (1996, Cell 86:599-606); Hanallah et al. (2004, J. Bone Joint Surg. 86 :80-91) ; and Glaser et al. (2003, J. Bone Joint Surg. 85 :2332-2342). Similarly, the prior art suggests that pre-treatment with noggin via gene therapy can protect against ossification upon subsequent treatment with a BMP-4 implant. See Hanallah et al. and Glaser et al., *supra*. .... The state of the prior art indicates that noggin may actually induce increased bone density and bone formation rates, which would not be

expected of a BMP-4 antagonist and is the opposite of the asserted therapeutic activity of noggin. See Yanagita, 2005, Cytokine and Growth Factor Reviews 16:309-317, particularly p. 314, second paragraph, first column. Furthermore, the art acknowledges that the developmental functions of BMPs have been extensively studied; however, the biological functions of BMPs after birth remain to be elucidated (*ibid.*, p. 314, last paragraph of second column). Such is also the case for noggin, a putative BMP antagonist. Thus, the state of the art shows the unpredictability of what therapeutic effect a BMP antagonist such as noggin would have in a patient after birth. Finally, the claims are extremely broad, with many claims not specifying the BMP-related disorder to be treated or the effect that noggin administration is expected to have.

Applicant argues that the legal standard for enablement relates to whether the disclosure, taken with knowledge available in the art, enables one of ordinary skill to make and use the claimed invention without undue experimentation. Applicant urges that the office action improperly implied that working examples were required. This has been fully considered but is not found to be persuasive. The previous Office Action did not require working examples. However, since the court in *In re Wands* stated that the presence or absence of working examples was one of the factors to be considered for enablement, it was pointed out in the rejection that no working examples were provided. However, the other factors were also discussed, including quantity of experimentation, amount of direction/guidance presented, nature or complexity of the invention, state of the prior art, unpredictability of the art, and breadth of the claims. See pp. 3-5, 8 of the previous Office Action.

Applicant points to paragraph [0065] and Glaser et al. (2003, J. Bone Joint Surg. 85A :2332-2342) as evidence that administration of noggin was effective in an animal model of BMP4-induced heterotopic ossification. This has been fully considered but is

not found to be persuasive. Paragraph [0065] and p. 2335 of Glaser et al. are essentially equivalent. These sections describe local delivery of NOG in an rhBMP2 implant to normal BALB/c male mice (Glaser et al., p. 2334, middle of right column). The NOG was not administered to the BMP4-induced heterotopic ossification model. Furthermore, the NOG was co-administered with rhBMP2, which is not the subject matter of the claims. It is noted that systemic administration of NOG was not effective in preventing BMP4-induced heterotopic ossification (Glaser et al., p. 2335, middle of right column), thus supporting the rejection.

Applicant argues that an inappropriately high standard of enablement was applied. Citing case law, Applicant urges that the specification need not re-teach what is already known in the art. Applicant concludes that those in the filed are aware of how to use protein therapeutics, how to determine formulations, doses, frequency of administration, etc., such that only routine experimentation is required. This has been fully considered but is not found to be persuasive. While there is no disagreement with Applicant's characterization of the case law, an objective consideration of the facts leads to the conclusion that undue experimentation would have been required. Yanagita (of record) reported that noggin induces bone growth, which is not the activity desired to treat diseases like FOP. Glaser et al. reported that systemic administration of NOG was not effective in preventing BMP4-induced heterotopic ossification. To solve these problems would have taken more than determination of formulation and dosage. it would have required undue experimentation.

Applicant argues that there is nothing unduly broad or unusual about the nature of the invention, since it is directed to treatment of disease related to BMP by administering a specific BMP antagonist. This has been fully considered but is not found to be persuasive. The amended claims are more narrow than the original claims in that the BMP antagonist is narrowly defined. However, the claims' recitation of a BMP-related disorder or condition still encompasses a very large patient population with diverse disease etiologies. For example, Waite et al. (2003, Nature Reviews Genetics 4(10):763-773) disclose that BMPs are involved in diseases as diverse as cancers, vascular diseases, and gastrointestinal disorders. It is noted that "BMP-related disorders" can be caused by too much BMP activity or too little BMP activity. It is unclear how a BMP antagonist could be used to treat a disease characterized by too little BMP activity.

Applicant argues that the specification's teachings can be applied without undue experimentation, including the teaching that noggin was used in an *in vivo* mouse model. This has been fully considered but is not found to be persuasive because, as discussed above, there is evidence that administration of NOG to a patient suffering from BMP4-induced heterotopic ossification is not effective (Glaser et al.), and noggin has bone induction activity (Yanagita). Furthermore, there is evidence that BMPs are involved in diverse diseases (Waite et al.), and it is not clear how noggin could be used to treat the same.

Applicant argues that the examiner has not provided a rational basis to doubt the specification's statements that noggin, a BMP antagonist, could be used to treat BMP-

related disorders. This has been fully considered but is not found to be persuasive. As discussed above, a rational basis has been established, even for the preferred embodiment of treating FOP. Furthermore, it is unclear how a BMP antagonist can be used to treat a BMP-related disease characterized by too little BMP or by too little BMP activity.

Applicant takes issue with the examiner's reliance on Yamagita rather than on the evidence in the specification and Glaser et al. This has been fully considered but is not found to be persuasive. As discussed above, the specification and Glaser et al. describe local delivery of NOG in an rhBMP2 implant to normal BALB/c male mice (Glaser et al., p. 2334, middle of right column). The NOG was not administered to the BMP4-induced heterotopic ossification model. Furthermore, the NOG was co-administered with rhBMP2, which is not the subject matter of the claims. It is noted that systemic administration of NOG was not effective in preventing BMP4-induced heterotopic ossification (Glaser et al., p. 2335, middle of right column), thus supporting the rejection. Yamagita provides further evidence about the activity of noggin on bone.

Applicant argues that they are not required to disclose or teach all side effects of a pharmacologically effective agent. This has been fully considered but is not found to be persuasive. While the specification need not disclose all side effects, it must disclose how to make and use the invention. In view of the evidence, especially the specification itself and the Glaser et al., Yamagita, and Waite et al. references, this has not been accomplished.

Applicant is advised that submission of any data generated after the filing date wherein noggin polypeptides were used to treat BMP-related disorders in subjects suffering from BMP-related disorders would be considered probative evidence. Such evidence should be submitted as a publication or under 37 CFR 1.132. Applicant is advised that such would be considered even if submitted after final.

Due to the large quantity of experimentation necessary to determine how to use noggin polypeptides therapeutically to treat BMP-related disorders, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the effects of BMPs or BMP antagonists when administered after birth, and the breadth of the claims which fail to recite limitations regarding what disease should be treated and what effect is to be expected, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

Elizabeth C. Kemmerer

ELIZABETH C. KEMMERER, PH.D.
PRIMARY EXAMINER